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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,683	SCHWENK ET AL.	
	Examiner	Art Unit	
	MICHAEL WILSON	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-19,24,25,28-30,32-41,43-52 and 56-58* is/are pending in the application.

4a) Of the above claim(s) *47 and 49-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19,24,25,28-30,32-41,43-46,48 and 56-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16, 20-23, 26, 27, 31, 42, 53-55, have been canceled. Claims 17-19, 24, 25, 28-30, 32-41, 43-52, 56-58 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 3-8-11 have been fully considered but they are not persuasive.

Please do not use bold face type in amendments. Simply underline and strike.

Election/Restrictions

Claims 47 and 49-52 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 1-28-08.

Claims 17-19, 24, 25, 28-30, 32-41, 43-46, 48, 56-58 are under consideration.

Claim Objections

The abbreviations in claim 33 "CAGGS, hCMV, PGK, FABP, Lck, CamKII, CD19... ...aP2... ...MCK, MyHC, WAP, Col2A, Mx, tet and trex" have been spelled out first and then abbreviated (i.e. human cytomegalovirus (hCMV)).

Claim 33 is objected to as amended because "selected from the group consisting of... ...promoters" is grammatically incorrect.

Claim Rejections - 35 USC § 112

New Matter

Claims 56 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "Rosa26 locus" has support on pg 8, lines 1-2.

The rejections of claims 53-55 under new matter have been withdrawn because the claims have been canceled.

Claim 56, step b), remains new matter. Pg 9, last three lines, states: "a donor DNA comprising the same two mutually incompatible first RRSs contained in the acceptor DNA by utilizing a recombination vector as defined above". Original claim 7, step a) states: "a donor DNA comprising the same two mutually incompatible first RRSs contained in the acceptor DNA by utilizing a recombination vector as defined in claims 2 to 4". However, step b) requires "(b) introducing a recombination vector comprising a functional DNA sequence into the acceptor DNA-modified eukaryotic cell, the functional DNA sequence in the recombination vector being donor DNA flanked by two mutually incompatible RRSs that are identical to the two mutually incompatible RRSs in the acceptor DNA". Pg 9 and original claim 7 do not contemplate a recombination vector comprising a "functional DNA sequence", that the two RSSs "flank" the donor DNA or that the two RSSs are identical to the RSSs of step a) as claimed. It is not readily apparent applicants contemplated the step now claimed. Applicants point to page 9 and pg 4 which describe "recombinase mediated

recombination" but do not specifically imply "(b) introducing a recombination vector comprising a functional DNA sequence into the acceptor DNA-modified eukaryotic cell, the functional DNA sequence in the recombination vector being donor DNA flanked by two mutually incompatible RRSs that are identical to the two mutually incompatible RRSs in the acceptor DNA" as claimed. Applicants point to original claim 7 which does not teach the limitations claimed. Clarification is required.

Indefiniteness

Claims 17-19, 24, 25, 28-30, 32-46, 56-58 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claim 55 has been withdrawn because the claim has been canceled.

Claim 17 remains indefinite because "a modified Rosa26 locus" does not make sense. A locus is a position on a chromosome. While the structure of the gene may be modified, those of skill would not modify the position of Rosa26. "Wherein said promoter is heterologous to the Rosa26 locus" does not make sense either because a promoter may be heterologous to other DNA sequences but not to a position on a chromosome.

Applicants argue the locus refers to a specific stretch of nucleotides on a chromosome. Applicants' argument is not persuasive. Applicants' definition cannot be found anywhere in the literature or the specification. The term refers to a position, not a nucleic acid sequence (see Biology Online definition of "locus", 2011). At best, the term

may refer to the position of a stretch of nucleotides on a chromosome, which still makes the phrase indefinite because applicants are not modifying the position of the nucleotides. A recommendation to overcome the rejection cannot be made without a better understanding of the intention of the claim. If the specification supports modifying a Rosa26 "gene", that language would be clear; however, support for Rosa26 "gene" is not explicit in the specification. Applicants could possibly explain why the specification implies the "Rosa26 gene" and provide references that show the art at the time of filing had knowledge of the Rosa26 gene, which could possibly overcome this rejection. If applicants intend the claim to mean modifying a stretch of nucleotides in a locus, the locus should be set forth somehow, and the claim should indicate modifying a nucleic acid sequence in locus; however, such an amendment cannot be envisioned by the examiner at this time.

The metes and bounds of what applicants consider an "inducible ubiquitous promoter" and "inducible tissue specific promoter" in claim 32 remain indefinite. The structure of such promoters is not defined in the specification or the art at the time of filing. Applicants argue those of skill would know what the phrase meant. Applicants' argument is not persuasive. While the specification need not define the phrase, those of skill would have to look to the art at the time of filing to determine the meaning; however, the art at the time of filing did not define which promoters are "inducible ubiquitous promoters" and "inducible tissue specific promoters". Without providing a definition for the phrases that were known in the art at the time of filing, the phrases

have no definition, and those of skill would not have known when they were infringing on the claim.

Claim 45 remains indefinite because it is unclear what applicants consider an "inactive" positive selection marker. Applicants point to "Fukushige at ID, 7905, left column, last paragraph" which refers to "an inactive lox-neo-fusion gene that is integrated by cre-mediated integration yielding a function ATG-lox neofusion gene in the cell". Applicants' argument is not persuasive. It is unclear the "lox-neo fusion gene" of Fukushige on pg 7905, col. 1, last 5 lines is an "inactive positive selection marker", Fukushige does not define an "inactive positive selection marker," Fukushige does not teach other "inactive positive selection markers", and applicants do not define what they consider an "inactive positive selection marker". Without such guidance in the art at the time of filing or in the specification as originally filed, the phrase remains indefinite.

Claim 56 remains indefinite because the metes and bounds of what applicants consider "two mutually incompatible first RRSs" does not clearly set forth the structure or function of the acceptor DNA. Pg 9 uses the phrase (last 5 lines) and pg 10, first four lines, use the term RSS, but the metes and bounds the phrase are unclear. Using the phrase does not mean the phrase is defined. Applicants have not disclosed the structure or function of "two mutually incompatible first RRSs" on pg 9, 10 or any where else in the specification. Without such guidance, those of skill would not know when they were infringing on the claim. Claims 43-45 are included because they are dependent upon claim 56. Furthermore, it is unclear how "two" RRSs can both be "first" as claimed. Applicants point to Schlake. Applicants' argument is not persuasive.

Schlake has been reviewed, but does not use the phrase in question or define the phrase.

Claim Rejections - 35 USC § 102

Claims 17-25, 28-30, 32-32, 34-38, 43-46, 48 and 56 remain rejected under 35 U.S.C. 102(b) as being anticipated by Soprano (WO99/53017) for reasons of record.

Soriano made a Rosa26 transgenic mouse by introducing a DNA cassette comprising a LacZ gene flanked by loxP sites into the Rosa26 gene of a mouse ES cell and implanting the ES cell into a mouse blastocyst. The LacZ gene was under the control of the mouse Rosa26 promoter (Example 1, pg 30) and is considered a "selectable marker" gene as newly amended. Soriano also taught making a Rosa26Cre transgenic mouse (Example 2, pg 41) by introducing a construct into ES cells, the construct comprising a deletor cassette comprising a recombinase gene operably linked to an upstream splice acceptor (SA and a downstream polyA sequence with a positive selection cassette comprising a PGK promoter, the neo gene and a polyadenylation sequence (pg 7, lines 2-10). The construct was inserted into the targeting vector comprising homology arms for the Rosa26 gene and a diphtheria toxin gene for negative selection (pg 7, line 9-10; pg 7, line 1-2). Soriano also made a transgenic mouse by introducing a targeting vector into mouse ES cells, the vector comprising a reporter cassette comprising a splice acceptor operably linked to stuffer DNA flanked by two loxP sites (pg 7, lines 10-16); the stuffer DNA comprised a PGK promoter, the neo gene and four polyA sites (pg 44, Example 3). The coding sequence described by

Soriano is a "DNA sequence which can be converted into such gene expression cassette."

The cassette comprises a gene of interest operably linked to a PGK promoter (Fig. 1C; Fig. 4), which is "heterologous to the Rosa26 locus" as claimed. In the alternative, Soriano taught numerous Rosa26 promoter fragments including mutagenized promoters, (pg 34-35) which are "heterologous" as claimed because they are different in structure (especially the mutagenized Rosa26 promoter) than the original Rosa26 promoter (Heterologous is defined as "differing in structure and origin: describes organisms or parts that differ from each other in structure or origin" (Encarta Dictionary definition of "heterologous", 2010)). In a third alternative, Soriano taught "isogenic homology regions flank the exogenous targeting construct sequence that is to replace the targeted promoter gene locus sequence" (pg 26, lines 1-3, emphasis added), i.e. to replace the Rosa26 promoter with a heterologous promoter via recombination, which is equivalent to a promoter that is "heterologous to the Rosa26 locus" as claimed.

It is noted that "heterologous" means being from another tissue (Dorland Medical Dictionary definition of "heterologous", 2010) or "differing in structure and origin: describes organisms or parts that differ from each other in structure or origin" (Encarta Dictionary definition of "heterologous", 2010). "Heterologous" is not limited to "xenogeneic" (which means from another species).

The Rosa26 promoter fragments included mutagenized promoters, (pg 34-35) which they have a different structure than the original Rosa26 promoter. Heterologous

is defined as "differing in structure and origin: describes organisms or parts that differ from each other in structure or origin" (Encarta Dictionary definition of "heterologous", 2010).

The cassette comprises a gene of interest operably linked to a PGK promoter (Fig. 1C; Fig. 4), which is "heterologous to the Rosa26 locus" as claimed. Soriano also taught "isogenic homology regions flank the exogenous targeting construct sequence that is to replace the targeted promoter gene locus sequence" (pg 26, lines 1-3), i.e. to replace the Rosa26 promoter with a heterologous promoter using recombination, which is equivalent to a promoter that is "heterologous to the Rosa26 locus" as claimed.

Response to arguments

Applicants argue Soriano did not teach a selectable marker gene under the control of a promoter that is heterologous to the Rosa26 locus. Applicants' argument is not persuasive. Soriano taught making a Rosa26Cre transgenic mouse (Example 2, pg 41) by introducing a construct into ES cells, the construct comprising a deletor cassette comprising a recombinase gene operably linked to an upstream splice acceptor (SA and a downstream polyA sequence with a positive selection cassette comprising a PGK promoter, the neo gene and a polyadenylation sequence (pg 7, lines 2-10) (Fig. 1C, Fig. 3C). Soriano also taught "isogenic homology regions flank the exogenous targeting construct sequence that is to replace the targeted promoter gene locus sequence" (pg 26, lines 1-3, emphasis added), i.e. to replace the Rosa26 promoter with a heterologous promoter via recombination, which is equivalent to a promoter that is "heterologous to the Rosa26 locus" as claimed. These two promoters discussed by Soriano are clearly

within the realm of what applicants' arguments indicate is the intended meaning of the claims.

In addition, the phrase "promoter heterologous to the Rosa26 locus" can be interpreted broadly as any promoter that is "from another tissue" (Dorland Medical Dictionary definition of "heterologous", 2010) or "differing in structure and origin: describes organisms or parts that differ from each other in structure or origin" (Encarta Dictionary definition of "heterologous", 2010). "Heterologous" is not limited to "xenogenic" (which means from another species). Soriano taught the LacZ operably linked to non-native, mutagenized Rosa26 promoters meets which also meets the limitation claimed because they differ from the structure of the promoter in the original Rosa26 locus.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday through Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

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/Michael C. Wilson/
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